REMARKS

The Examiner is thanked for the opportunity provided to the applicants to meet and discuss the claimed invention in an interview dated January 10, 2007. The applicants have now amended claim 1 with the agreed upon amendment to place the claims in a condition of allowance. A declaration is provided asserting the requirement for a helicase in helicase-dependent amplification. (See Huimin declaration ¶ 2).

Claim 3 has been cancelled. Claims 1, 5 and 49 have been amended. New claim 51 has been added. No new subject matter is believed to have been added in the amendments. Support for "helicase-dependent reaction" to describe the improved amplification method is the focus of the entire application from the title, the abstract and all sections of the specification. While it is inherent in the claims as filed in view of the specification, the claims have been amended to include the terms so as to more distinctly define the invention.

Rejecton under 35 U.S.C. §102(e)

(a) Armes et al.

Claims 1-8, 12, 3, 29, 31-33, 40, 41 and 43-45 are rejected as anticipated by Armes et al. This reference describes a method of isothermal amplification that requires recA. RecA is not a helicase. (See definition on page 20 of the reference). The reference further describes auxilary enzymes, which can optionally be used to promote disassembly of recA from dsDNA.

The reference describes the auxiliary enzymes as including helicases (0032) to promote dissociation of the recA from DNA. There is no suggestion that the isothermal amplification method described by Armes is helicase dependent as required in the present claimed invention (see Huimin declaration, ¶ 2).

RecA is used in the reference to "invade double stranded DNA with single stranded homologous DNA" (abstract of the reference). This event occurs as a result of recA coating single stranded DNA to form a nucleoprotein primer. The nucleoprotein primers actually displace the complementary strands in a double stranded DNA. (See claim 1 of the reference).

> [RecA] coat single stranded DNA (ssDNA) to form filaments which then scan double-stranded DNA (dsDNA) for regions of sequence homology. When homologous sequences are located, the nucleoprotein filament strand invades the dsDNA creating a short hybrid and a displaced strand bubble known as a D-loop. [0008]

The reference describes recA as a recombinase agent as defined below:

> A recombinase agent is an enzyme that can coat single stranded DNA (ssDNA) to form filaments which can then scan double stranded DNA (dsDNA) for regions of sequence homology. (0027)

In the reference, the recombinase contacts a single stranded oligonucleotide.

In contrast, the present claimed method requires that the helicase preparation contact a template duplex nucleic acid.

In summary, the reference describes amplification that requires recA and optionally utilizes helicase as an accessory protein for purposes of binding to single strand oligonucleotide primers. In contrast, the present claimed method requires a helicase preparation to unwind duplex DNA.

(b) Dean et al.

Claims 49 and 50 have been rejected as anticipated by Dean et al. Claim 49 has been amended to more distinctly define the claimed method.

Claims 49 and 50 define "A method for determining whether a helicase is suited for exponentially and selectively amplifying a target nucleic acid...".

The Dean et al. reference describes multiple-displacement amplification and evaluates whether the polymerase (not a helicase preparation) can carry out strand-displacement replication using an assay citing Examples 1 and 5 (see col 24, line 40). Applicants have failed to find in Example 1 entitled "Whole Genome Amplification Using Nuclease-Resistant Hexamer Primers" (col 36-42), any assay for determining whether a particular helicase is suited for amplification. Indeed, this example describes the use of a single polymerase (phi 29 polymerase) in multiple displacement amplification without reference to any helicase. Similarly, in Example 5, entitled "Omission of DNA Template Incubation at 95°C results in increased Locus representation in DNA products Amplified by MDA", Applicants have not been able to

locate any description relating to a method for determining whether a helicase is suited for amplifying target nucleic acid.

The Examiner has cited column 24 of the reference in support of the rejection. Column 24 refers to a strand-displacement factor (lines 18-36), exemplified by " BMfrI polymerase accessory subunit, adenovirus DNA binding protein, herpes simplex viral protein ICP8, single stranded binding proteins, phage T4 gene 32 protein and calf thymus helicase". There is no suggestion in the reference that these proteins should be used in specific combinations that include a helicase and a single strand binding protein. Rather, the reference suggests that a single strand binding protein or calf thymus helicase can be used interchangeably.

In view of the above, the Examiner is respectfully requested to reverse the rejection of the claims under 35 U.S.C. §102(e).

Rejection of claims under 35 U.S.C. §102(b)

The Examiner has rejected claims 1-13, 29-33, 40, 42 and 44 under 35 U.S.C. §102(b) as being anticipated by Hogrefe et al.

The Hogrefe et al. reference describes generally enhancing nucleic acid polymerase reactions using factors cloned from the archaea-Pyrococcus furiosis. The reference states that these factors may be used to enhance isothermal amplification without further discussion or clarification (page 25). The reference additionally describes the optional use of helicases in PCR amplification. These reactions were carried out under standard conditions.

> PCR reactions were carried out under standard conditions..... PCRs using PfuTurbo or Taq2000 DNA polymerase were carried out with the PCR buffers provided with the enzyme (Stratagene)...Reactions were cycled in 200ul thin walled tubes using any of the following temperature cyclers...(Reference page 45, para 6, page 46).
>
> The addition of diluted preparations of helicase 2 or helicase dna2 to PCR reactions comprising Pfu polymerase can lead to increased PCR product yield. (Reference page 57).

There is no teaching in the Hogrefe reference that the presence of a helicase is required for amplification. Moreover, there is no teaching in the reference regarding the use of non-thermostable helicases. More particularly, there is no teaching that non-thermostable helicases should be combined with single strand binding proteins for any purpose. The helicase 2 and helicase dna2 are thermostable helicases.

The claimed method can be readily differentiated from Hogrefe because amplification is helicase dependent. Being "dependent" means that the helicase is required. The helicase does not merely enhance existing reaction conditions as described in Hogrefe where amplification can proceed in the absence of a helicase. In the claimed method, if there is no helicase, there is no detectable amplification using gel electrophoresis (see for example in the application, Figures 11, 13). There are some important advantages of the claimed method. For example, unlike the Hogrefe reference, the claimed helicase-dependent amplification does not utilize thermocycling.

> Regardless of the source of the target nucleic acid, a helicase preparation may be used to replace a heat denaturation step during amplification of a nucleic acid by unwinding a double stranded molecule to produce a single stranded molecule for polymerase dependent amplification without a change in temperature of reaction. Hence thermocycling that is required during standard PCR amplification using Taq polymerase may be avoided. (Page 30 of the application or para 0090 of the published application).

For the reasons provided above, applicants respectfully request that the Examiner reverse the rejection of the claims.

CONCLUSION

For the reasons set forth above, Applicants respectfully submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Applicants submit check in the amount of $100 for any extra independent claim. Applicants do not believe that any further fees are required, but authorize that any deficiencies be charged to Deposit Account No. 14-0740.

Respectfully submitted,

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